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422,699 17 October 1989 (17.10.89) US 483,913 22 February 1990 (22.02.90) US 569,920 20 August 1990 (20.08.90) US

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(54) Title: OSTEOGENIC DEVICES

(57) Abstract

Disclosed are 1) amino acid sequence data, structural features, and various other data characterizing a human of protein, OP1, 2) osteogenic devices comprising a heat treated xenogenic bone collagen matrix containing osteogenic promethods of producing osteogenic proteins using recombinant DNA technology and 4) use of osteogenic devices to mimic ural course of endochondral bone formation in mammals.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

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Pang, Roy H.L.

- (ii) TITLE OF INVENTION: Osteogenic Devices
- (iii) NUMBER OF SEQUENCE: 7
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 - (B) STREET: 60 State Street
 - (C) CITY: Boston
 - (D) STATE: Massachusetts
 - (E) COUNTRY: U.S.A.
 - (F) ZIP: 02109
- (v) COMPUTER READABLE FORM:
 - (A) MEDIUM TYPE: Diskette, 3.5 inch, 720kb storage
 - (B) COMPUTER: IBM XT
 - (C) OPERATING SYSTEM: DOS 3.30
 - (D) SOFTWARE: Word Perfect 5.0
- (vi) CURRENT APPLICATION DATA:
 - (B) FILING DATE: 20-Aug-90
- (vii) PRIOR APPLICATION DATA:
 - (A) APPLICATION NUMBER: US 422,699
 - (B) FILING DATE: 17-Oct-89
 - (C) APPLICATION NUMBER: US 483,913
 - (D) FILING DATE: 22-Feb-89

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 139 amino acids
 - (B) TYPE: amino acid
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

	(X 1)	BEQU	ENCE	DESCR	IPT10	n: be	Ö ID	wo:1:
Ser 1	Thr	Gly	Ser	Lys 5	Gln	Arg	Ser	Gln
Asn 10	Arg	Ser	Lys	Thr	Pro . 15		Asn	Gln
Glu	Ala 20	Leu	Arg	Met	Ala	Asn 25		Ala
Glu	Asn	Ser 30	Ser	Ser	Asp	Gln	Arg 35	Gln
Ala	Сув	Lys	Lys 40		Glu	Leu	Tyr	Val 45
	Phe		•	50	•		• .	
55	Ile	•			60			
	Ty r 65					70		
~	Pro	75			1	· . ·	80	
•	Asn		85	/x.s		٠		90
-	His		*********	95	.•	•	, , ,	
100	/)	1	` ;	105	•		Gln
Leu	Asn 110	Ala	Ile	Ser	Val	Leu 115	Tyr	Phe

Asp	Asp	Ser 120	Ser Asn	Val	Ile	Leu 125	Lys
Lys	Tyr		Asn Met	Val	Val	Arg	Ala 135
Cys	Gly	Cys	His.	•			

(2) INFORMATION FOR SEQ ID NO:2:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 132 amino acids
 - (B) TYPE: amino acid
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

		•						
					•		Ser 1	Gln
Asn	Arg	Ser 5	Lys	Thr	Pro	Lys	Asn 10	Gln
Gľu	Ala	Leu	Arg 15	Met	Ala	Asn	'Val	Ala 20
Glu	Asn	Ser	Ser	Ser 25		Gln	Arg	Gln
Ala 30	Cys	Lys	Lys	His	G1u 35	Leu	Tyr	Val
Ser	Phe 40	Arg	Asp	Leu	Gly	Trp 45	Gln	Asp
Trp	Ile	Ile 50	Ala	Pro	Glu	Gly	Tyr 55	Ala
Ala	Tyr	Tyr	Cys 60	Glu	Gly	Glu	Cys	Ala 65
Phe	Pro	Leu	Asn	6er 70	Tyr	Met	Asn	Ala

Thr 75	Asn	His	Ala		Val 80	Gln	Thr	Leu
Val	His 85	Phe	Ile	Asn		Glu 90	Thr	Val
Pro	Lys	Pro 95	Сув	Cys	Ala	Pro	Thr 100	Gln
Leu	Asn	Ala	11e 105	Ser	Val	Leu	Tyr	Phe 110
Asp	Asp	Ser	Ser		Val		Leu	Lys
Lys 120	Tyr	Arg	Asn	Met	Val 125		Arg	Ala
Cys	Gly 130	Cys	His.			•		

(2) INFORMATION FOR SEQ ID NO:3:

- (1) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 119 amino acids
 - (B) TYPE: amino acid
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Leu 1	Arg	Met	Ala	Asn 5	Val	Ala	Glu	Asn
Ser 10	Ser	Ser	Asp	Gln	Arg 15	Gln	Ala,	Сув
Lys	Lys 20	His	Glu	Leu	Tyr	Val 25	Ser	Phe
Arg	Asp	Leu 30	Gly	Trp	Gln	Asp	Trp	
Ile	Ala	Pro	G1u 40	Gly	Tyr	Ala	Ala	Tyr 45

Tyr	Cys	Glu	Gly	Glu 50	Сув	Ala	Phe	Pro
Leu 55	Asn	Ser	Tyr	Met	Asn 60	Ala	Thr	Asn
His	Ala 65	Ile	Val	Gln	Thr	Leu 70	Val	His
Phe	Ile	Asn 75	Pro	Glu	Thr	Val	Pro 80	Ĺys
Pro	Сув	Cys	Ala 85	Pro	Thr	Gln	Leu	Asn 90
Ala	Ile	Ser	Val	Leu 95	Tyr	Phe	Asp	Asp
Ser 100	Ser	Asn	Val	Ile	Leu 105	Lys	Lys	Tyr
Arg	Asn 110		···Val	Val	Arg	Ala 115	Сув	Gly
Cys	His	•	. '	•			:	

(2) INFORMATION FOR SEQ ID NO:4:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 117 amino acids
 - (B) TYPE: amino acid
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

•		Met 1	Ala	Asn	Val	Ala 5	Glu	Asn
Ser	Ser	Ser 10	Asp	Gln	Arg	Gln	Ala 15	Сув
Lys	Lys	His	Glu 20	Leu	Tyr	Val	Ser	Phe 25
Arg	Asp	Leu	Gly	Trp	Gln	Asp	Trp	Ile

Ile 35	Ala	Pro	Glu	Gly	Tyr 40	Ala	Ala	Tyr
Tyr	Cys 45	Glu	Gly	Glu	Cys	Ala 50	Phe	Pro
Leu	Asn	Ser 55	Tyr	Met	Asn	Ala	Thr 60	Asn
His	Ala	Ile	Val 65	Gln	Thr	Leu	-Val	His 70
Phe	Ile	Asn	Pro.	Glu 75	Thr	Val	Pro	Lys
Pro 80	Cys	Cys	Ala	Pro	Thr 85	Gln	Leu	Asn
Ala	Ile 90	Ser	Val	Leu	Tyr	Phe 95	Asp	Asp
Ser	. Ser	Asn 100	Val	Ile	Leu	Lys	Lys 105	Tyr
Arg	Asn	Met	Val 110	Val	Arg	Ala	Cys	Gly 115
Сув	His				•	٠.	٠.	

(2) INFORMATION FOR SEQ ID NO:5:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 116 amino acids
 - (B) TYPE: amino acid
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Ala Asn Val Ala Glu Asn
1 5

Ser Ser Ser Asp Gln Arg Gln Ala Cys
10 15

Lys Lys His Glu Leu Tyr Val Ser Phe

Arg 25	Asp	Leu	Gly	Trp	Gln 30	Asp	Trp	Ile
Ile	Ala 35	Pro	Glu	Gly	Tyr	Ala 40	Ala	Tyr
Tyr .	Cys	Glu 45	Gly	Glu	Сув	Ala	Phe 50	Pro
Leu	Asn	Ser	Tyr 55	Met	Asn	Ala	Thr	Asn 60
His	Ala	Ile	Val	Gln 65	Thr	Leu	Val	His
Phe=	-Ile	Asn .	Pro	Glu	Thr 75	Val	Pro	Lys
Pro	Cys 80	Сув	Ala	Pro	Thr	Gln 85	Leu	Asn
Ala	Ile	Ser 90	Val	Leu	Tyr	Phe	Asp 95	Asp
Ser	Ser	Asn	Val 100	Ile	Leu	Lys	Lys	Tyr 105
ytd	Asn	Met	Val	Val 110	Arg	Ala	Cys	Gly
Cys	His	•.	•	•	. =			,
115		•						

(2) INFORMATION FOR SEQ ID NO:6:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 114 amino acids
 - (B) TYPE: amino acid
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Val	Ala	Glu	Asn	Ser 5	Ser	Ser	Asp	Gln
Arg 10	Gln	Ala	Сув	Lys	Lys 15	His	Glu,	Leu
Tyr	Val 20	Ser	Phe	Arg.	Asp	Leu 25	_	Trp
Gln	Asp	Trp 30	Ile	Ile	Ala	Pro	Glu 35	Gly
Tyr	Ala	Ala	Tyr 40	Tyr	Cys	Ģlu	Gly	Glu 45
Cys	Ala	Phe	Pro	Leu 50		Ser	Tyr	Met
Asn 55		Thr	Asn	His	Ala 60	Ile	Val	Gln
Thr	Leu 65	Val	His	Phe	Ile	Asn 70	Pro	Glu
Thr	Val	Pro 75	_	Pro	Сув	Cys	Ala 80	Pro
Thr	Gln	Leu	Asn 85	Ala	Ile	Ser	Val	Leu 90
Tyr	Phe	Asp	Asp	Ser 95	Ser	Asn	Val	Ile
Leu 100	Lys	Lys	Tyr	Arg	Asn 105	Met	Val	Val
Arg	Ala 110	Сув	Gly	Cys	His	•	. <u>.</u>	

(2) INFORMATION FOR SEQ ID NO:7:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1822 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA	
(iii) HYPOTHETICAL: no	
(iv) ANTI-SENSE: no	•
(vi) ORIGINAL SOURCE:	
(A) ORGANISM: Bovinae	·
(F) TISSUE TYPE: bone	
(vii) IMMEDIATE SOURCE:	
(A) LIBRARY: human placenta	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:	7:
GGTGCGGGCC CGGAGCCCGG AGCCCGGGTA GCGCGTAGAG	40
CCGGCGCG ATG CAC GTG CGC TCA CTG CGA GCT GC	G 75
Met His Val Arg Ser Leu Arg Ala Al	
1 5	
GCG CCG CAC AGC TTC GTG GCG CTC TGG GCA CCC	108
Ala Pro His Ser Phe Val Ala Leu Trp Ala Pro	
10 15 20	
CTG TTC CTG CTG CGC TCC GCC CTG GCC GAC TTC	141
Leu Phe Leu Leu Arg Ser Ala Leu Ala Asp Phe	
25 30	•
AGC CTG GAC AAC GAG GTG CAC TCG AGC TTC ATC	174
Ser Leu Asp Asn Glu Val His Ser Ser Phe Ile	
35 40	
CAC CGG CGC CTC CGC AGC CAG GAG CGG CGG GAG	207
His Arg Arg Leu Arg Ser Gln Glu Arg Arg Glu	• ?
45 50	
ATG CAG CGC GAG ATC CTC TCC ATT TTG GGC TTG	240
Met Gln Arg Glu Ile Leu Ser Ile Leu Gly Leu	ı , ,
55 60	
CCC CAC CGC CCG CGC CAC CTC CAG GGC AAC	273
Pro His Arg Pro Arg Pro 1:is Leu Gln Gly Lys	
65 70 75	;

							•					
CAC	A.	AC	TCG	GCA	CCC	ATG	TIC	ATG	CIG	GAC	CTG	306
His	As	sn	Ser	Ala	Pro 80	Met	Phe	Met	Leu	Asp 85	Leu	
TAC	. AJ	AC.	GCC	ATG	GCG	GTG	GAG	GAG	GGC.	GGC	GGG .	339
Туг	As	sn	Ala	Met 90	Ala	Val	Glu	Glu	Gly 95	Gly	Gly	
CCC	: G(3C	GCC	CAG	GGC	TTC	TCC	TAC	CCC	TAC	AAG	372
Pro	G:		Gly 100	Gln	Gly	Phe	Ser	Tyr 105	Pro	Tyr	Lys	
GCC	: G:	rc	TTC	AGT	ACC	CAG	GGC	CCC	CCT	CTG	GCC	·· 405
Ala		al 10	Phe	Ser	Thr	Gln	Gly 115	Pro	Pro	Leu	Ala	
AGO	: C	ŤG	CAA	GAT	AGC	CAT	TTC	CTC	ACC	GAC	GCC	438
Se	L	eu	Gln	Asp	Ser			Leu	Thr	Asp	Ala.	
120				•		125	•			*	130	4.77
											GAA	471
**					-135	. •			•	140	•	
												504
Hi	вА	ga	Lys	G1u 145		Phe	His	Pro	Arg. 150		His	
CA	T C	GA	GAG	TTC	CGG	TTI	GAT	CTI	TCC	AAG	ATC	537
Hi	s A	rg	Glu 155		Arg	Phe	Asp	Lev 160		Lys	Ile	
CC	A G	AA	GGG	GAA	GCI	GTC	ACC	GCA	GCC	GAA	TTC	570
	0 0		Gly					Ale			Phe	
CG	G A	\TC	TAC	: AAC	GAC	TAC	TA C	CGC	GA	CGC	TTC	603
 አ ፣ 17		lle	"Ty:	Lys	a_Ası	Ty:		Arg	g Glu	Arg	Phe 185	
G.A	C	\AT	GAC	ACC	TTC	CGC	3 ATC	C AGO	GTI	TAT	CAG	636
						a Arg					Gln	
GI	:G (CTC	CA	GA(G CAC	TT	G GG	C AG	G GA	A TC	GAT	669

						-						
•	Val	Leu	Gln	Glu 200	His	Leu	Gly	Arg	Glu 205	Ser	Asp	
(CTC	TTC	CTG	CTC	GAC	AGC	CGT	ACC	CTC	TGG	GCC	702
,	Leu	Phe	Leu 210	Leu	Asp	Ser	Arg	Thr 215	Leu	Trp	Ala	
	TCG	GAG	GAG	GGC	TGG	CTG	GTG	TTT	GAC	ATC	ACA	735
	Ser	Glu 220	Glu	Gly	Trp	Leu	Val 225	Phe	Asp	Ile	Thr	f' .
	GCC	ACC	AGC	AAC	CAC	TGG	GTG	GTC	AAT	CCG	CGG	768
	Ala 230	Thr	Ser	Asn	His	Trp 235	Val	Val	Asn	Pro	Arg 240	•
	CAC	AAC	CTG	GGC	CTG	CAG	CTC	TCG	GTG	GAG	ACG	801
,	His		Leu	Gly		Gln					Thr	
				-	AGC	ATC	AAC	CCC	AAG	TTG	GCG	834
										Leu	Ala	
	GGC	CTG	ATT	GGG	CGG	CAC	GGG	CCC	CAG	AAC	AAG	867
				Gly					Gln		Lys	
	CAG	CCC	TTC	ATG	GTG	GCI	TTC	TTC	: AAG	GCC	: ACG	900
٠	Gln	Pro 275		Met	Val	Ala	280		Lys,	Ala	Thr	
	GAG	GTC	CAC	TTC	CGC	AGC	ATC	CGG	TCC	ACG	GGG	933
	Glu 285		·His	Phe	Arg	Ser 290		Arç	Se I	Thi	Gly 295	
	AGC	. AAA	CAG	CGC	: AGC	CAG	AAC	: CGC	TCC	AAC	ACG	966
	Ser	Lys	Glr	Arg	300		Asr	Arq	j Sei	1 Lys	Thr	•
	CCC	: AAG	AAC	CAC	GAJ	GCC	CTC	G CG	S ATC	3 GCC	AAC	999
11		Lys	ASI	1 Glr 310		ı Ala	Let	a Arq	31!		Asn	
•,	GT	GC/	A GAC	S AAC	AGO	C AGO	C AGO	GA	C CA	3 AGC	G CAG	. 1032

Val Ala Glu Asn Ser Ser Ser Asp Gln Arg Gln 320 325	
GCC TGT AAG AAG CAC GAG CTG TAT GTC AGC TTC	1065
Ala Cys Lys Lys His Glu Leu Tyr Val Ser Phe 330 335	
CGA GAC CTG GGC TGG CAG GAC TGG ATC ATC GCG	1098
Arg Asp Leu Gly Trp Gln Asp Trp Ile Ile Ala	
340 345 350	٠.
CCT GAA GGC TAC GCC GCC TAC TAC TGT GAG GGG	1131
Pro Glu Gly Tyr Ala Ala Tyr Tyr Cys Glu Gly	•
355 360	
GAG TGT GCC TTC CCT CTG AAC TCC TAC ATG AAC	1164
Glu Cys Ala Phe Pro Leu Asn Ser Tyr Met Asn	
365 370	•
GCC ACC AAC CAC GCC ATC GTG CAG ACG CTG GTC	· · ·
Ala Thr Asn His Ala Ile Val Gln Thr Leu Val	
CAC TTC ATC AAC CCG GAA ACG GTG CCC AAG CCC	1230
His Phe Ile Asn Pro Glu Thr Val Pro Lys Pro	
385 390	
TGC TGT GCG CCC ACG CAG CTC AAT GCC ATC TCC	1263
Cys Cys Ala Pro Thr Gln Leu Asn Ala Ile Ser	
395 400 409	•
GTC CTC TAC TTC GAT GAC AGC TCC AAC GTC ATC	
Val Leu Tyr Phe Asp Asp Ser Ser Asn Val Ile 410 415	•
CTG AAG AAA TAC AGA AAC ATG GTG GTC CGG GCG	1329
Leu Lys Lys Tyr Arg Asn Met Val Val Arg Ala 420 425	
TGT GGC TGC CAC TAGCTCCTCC GAGAATTCAG	1361
Cys Gly Cys His	
430	
ACCCTTTGGG GCCAAGTTTT TCTGGATCCT CCATTGCTC	G 1401

CCTTGGCCAG	GAACCAGCAG	ACCAACTGCC	TTTTGTGAGA	1441
CCTTCCCCTC	CCTATCCCCA	ACTTTAAAGG	TGTGAGAGTA	1481
TTAGGAAACA	TGAGCAGCAT	ATGGCTTTTG	ATCAGTTTTT	1521
		CAAGATCCTA	CAAGCTGTGC	1561
	TAGCAGGAAA	AAAAAACAAC	GCATAAAGAA	1601
AAATGGCCGG	GCCAGGTCAT	TGGCTGGGAA	GTCTCAGCCA	1641
TGCACGGACT	CGTTTCCAGA	GGTAATTATG	AGCGCCTACC	1681
AGCCAGGCCA	CCCAGCCGTG	GGAGGAAGGG	GGCGTGGCAA	1721
GGGTGGGCA	CATTGGTGTC	TGTGCGAAAG	GAAAATTGAC	Ì761
CCGGAAGTTC	CTGTAATAAA	TGTCACAATA	AAACGAATGA	1801
ATGAAAAAA	*****	A		1822

What is claimed is:

1. An osteogenic device for implantation in a mammal, the device comprising:

a biocompatible, in vivo biodegradable matrix of mineral-free, delipidated Type I insoluble bone collagen particles, depleted in noncollagenous protein; and

a protein produced by the expression of recombinant DNA in a mammalian host cell, the protein comprising two oxidized subunits, the amino acid sequence of each subunit being sufficiently duplicative of the amino sequence (Seq. ID No.6):

OP1-16V

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		. •							70			_		_	
G	Y	A	A	Y	Y	C	E	G	E	C	A	F	P	L	
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V	H	F			-	E	•	•	-	••	•	•			
				110					•				_ •	120	
P	T	Q	T.	N	λ	I	8	V	L	Y	F	D	D	S	
•	•	M	_		••	_			130	_					
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8	N	V	I	L	K	K	Y	R	N	M	V	V	R	A	
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C	G	C	H	•	٠.										

such that the dimeric species comprising said subunits has a conformation that is capable of inducing endochondral bone formation in a mammal when disposed within said matrix and implanted in said mammal.

2. An osteogenic protein expressed from recombinant DNA in a mammalian host cell and capable of inducing endochondral bone formation in a mammal when disposed within a matrix implanted in said mammal;

a protein produced by the expression of recombinant DNA in a mammalian host cell, the protein comprising two oxidized subunits, the amino acid sequence of each subunit being sufficiently duplicative of the amino sequence (Seq. ID No.6):

OP1-16V

			•											30
										V	A	E	N	S
									40					
S	S	D	Q	R	Q	A	C	K	K	H	E.	· L	Y	V
_	_		-	50	_						•	•		60
S	F	R	D		G	W	Q	D	W	I	I	A	P	E
	-	-	-				,	•	70		•			
G	Y	A	A.	Y	Y	C	E	G	E	C	A	· F	P	L
•	_			80	,		•			:	•			90
N	5	Y	M		A	T	N	H	A	I	V	Q	T	L
	_	-							.00			•		
v	H	F	I	N	P	E	T	V	P	K	P	C	C	À
••		_		.10									-	120
P	T	Q	L	N	A	I.	5	V	L	Y	F	D	D	8
	_	-					•		130			. •		
8	N	V	I	L	K	K	Y	R	N	M	V	V	R	A
C	G	C	Н,	,		·				٠,	•			•

such that the dimeric species comprising said subunits has a conformation that is capable of inducing endochondral bone formation in a mammal when disposed within said matrix and implanted in said mammal.

3. The invention of claim 1 or 2 wherein the amino acid sequence of each said subunit has at least 70% homology with the amino acid sequence (Seq. ID No.6):

OP1-16V

- 30
 V A E N S
 40
 S S D Q R Q A C K K H E L Y V
 50
 S F R D L G W Q D W I I A P E
 70
 G Y A A Y Y C E G E C A F P L
 80
 N S Y M N A T N H A I V Q T L
 100
 V H F I N P E T V P K P C C A
 110
 P T Q L N A I S V L Y F D D S
 S N V I L K K Y R N M V V R A
 C G C H.
- 4. The invention of claim 1 or 2 wherein the amino acid sequence of each said subunit has at least 80% homology with the amino acid sequence (Seq. ID No.6):

OP1-16V

30 V A E N S 40 S S D Q R Q A C K K H E L Y V 50 S F R D L G W Q D W I I A P E 70 G Y A A Y Y C E G E C A F P L

			80										90
S	Z	M	N	A:	T	N	H	λ	I	V	Ç	T	L
	•					-	1	.uu		• .			
H	P	I	N	P	E	T	V	P	K	P	C	C	λ
	-	1	10	_			•	•				1	.20
T	O	T.	N	À	I	S	V	L	Y	F	D	D	. S
•	*	_	-		_		1	130					~
14	V	Ť	L	ĸ	K					V	V	R	A
	•	-	_	•	-			_					
G	_	н		•				•	•				
	H T N	H F T Q N V	S Y M H F I T Q L	H F I N 110 T Q L N N V I L	S T M N A H F I N P 110 T Q L N A	S Y M N A T H F I N P E 110 T Q L N A I N V I L K K	S Y M N A T N H F I N P E T 110 T Q L N A I S N V I L K K Y	S Y M N A T N H H F I N P E T V 110 T Q L N A I S V N V I L K K Y R	S Y M N A T N H A 100 H F I N P E T V P 110 T Q L N A I S V L 130 N V I L K K Y R N	S Y M N A T N H A I 100 H F I N P E T V P K 110 T Q L N A I S V L Y 130 N V I L K K Y R N M	S Y M N A T N H A I V 100 H F I N P E T V P K P 110 T Q L N A I S V L Y F 130 N V I L K K Y R N M V	S Y M N A T N H A I V Q H F I N P E T V P K P C 110 T Q L N A I S V L Y F D 130 N V I L K K Y R N M V V	S Y M N A T N H A I V Q T H F I N P E T V P K P C C 110 T Q L N A I S V L Y F D D N V I L K K Y R N M V V R

5. The invention of claim 1 or 2 wherein the amino acid sequence of each said subunit comprise (Seq. ID No. 6):

OP1-16V

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C	G	C	н.	,				•	•			•		1	

6. The invention of claim 1 or 2 wherein to amino acid sequence of said subunit comprises (So ID No.1):

OP1-18

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S	N	V	I	L	K	K	Y	R	N	M	V	V	R	A
C	G	C	н.	•								•		. •

7. The invention of claim 1 or 2 wherein the amino acid sequence of each said subunit comprises (Seq. ID No. 2):

OP1-168

30 K - Q---R----Q----A--- C. K K I E L 70 · G Y C E Ħ N 100 120 110 130 R . N

8. The invention of claim 1 or 2 wherein the amino acid sequence of each said subunit comprises (Seq. ID No. 3):

OP1-16L

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V	H	F		N 110	P	E	T	-		K	P	C		A 120
P	T	Q	-	N	A	I	8		L. 130	. 4		D		
8	n	V	I	L	K	K	Y			, M	7	V	R	A
С	G	C	H	•		•			.;	•	•		•	٠.

9. The invention of claim 1 or 2 wherein the amino acid sequence of each of said subunit comprises (Seq. ID No. 4):

OP1-16M

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E	TCG S	GATCT(CTTC	68 CTGC L	O TCGA L D	CAGO	690 CGT R	ACC	CTC	700 TGGG W	L Q CCTC A S	71 GGAGG E	LO BAGGO E	CTGG
E	S	GATCTO D L 730	CTTC F	68 CTGC L 74	0 TCGA L D	CAGO S	690 CGT R 750	ACC	CTC	700 TGGG W 760	L Q CCTC A S	71 GGAGG E 77	LO BAGGO E (SCTGG(
E GT	S TTT	GATCTO D L 730 GACATO	CTTC F CACA	68 CTGC L 74 AGCCA	TCGA L D 0 .CCAG	CAGO S CAAO	690 CGT R 750 CAC	ACC	CCTC L SGTG	700 TGGG W 760 GTCA	L Q CCTC A S ATCC	GGAGG E 77 GCGGG	LO BAGG(E (70 BACA)	SCTGG(S W
E GT	S TTT	GATCT(D L 730 GACAT(D I	CTTC F CACA	68 CCTGC L 74 AGCCA A	O TCGA L D O CCAG T S	CAGO S CAAO	690 CGT R 750 CCAC	ACC T	CTC L SGTG V	700 TGGG W 760 GTCA V	L Q CCTC A S ATCC N P	GGAGG E 77 GCGGG R	LO BAGGO E (70 BACA) H I	SCTGG(S W ACCTG(N L
GTG V	S TTI F	GATCTO D L 730 GACATO D I 790	EACA T	68 CCTGC L 74 AGCCA A 80	O TCGA L D O CCAG T S	CAGO S CAAO N	690 R 750 CAC H 810	ACC T	CCTC L SGTG V	700 TGGG W 760 GTCA V 820	CCTC A S ATCC N P	GGAGG E 77 GCGGG R 83	LO BAGGO E (70 CACA) H 1	SCTGG(S W ACCTG(N L
GTG V	S TTI F SCAG	GATCTO D L 730 GACATO D I 790 GCTCTCO	CTTC F CACA T	68 CCTGC L 74 AGCCA A 80 GGAGA	O TCGA L D O CCAG T S O	CAGO S CAAO N GGAI	690 R 750 CAC H 810	TGG	ECTC L EGTG V EAGC	700 TGGG W 760 GTCA V 820 ATCA	CCTC A S ATCC N P	GGAGG E 77 GCGGG R 83 CAAG1	LO BAGGG E (70 BACA) H 1 BO	SCTGGC S W ACCTGC N L
GTG V	S TTI F SCAG	GATCTO D L 730 GACATO D I 790 CCTCTCO L S	CTTC F CACA T	68 CCTGC L 74 AGCCA A 80 GGAGA	TCGA L D CCAG T S CGCT	CAGO S CAAO N GGAI	690 R 750 CAC H 810 GGGG	TGG W CAG	ECTC L EGTG V EAGC	700 TGGG W 760 GTCA V 820 ATCA	CCTC A S ATCC N P ACCC	GGAGG E 77 GCGGG R 83 CAAG1	LO BAGGG E (70 CACA) H 1 BO TTGGG L 1	SCTGGC S W ACCTGC N L
GTG V CTG	STTI F SCAG	GATCTO D L 730 GACATO D I 790 GCTCTCO L S 850	CTTC F CACA T GGTC	68 CCTGC L 74 AGCCA A 80 GGAGA E 86	O TCGA L D O CCAG T S O CGCT T L	CAGO S CAAO N GGAT	690 CGT R 750 CCAC H 810 GGG 6	TGG W CAG	GTG L GTG V BAGC	700 TGGG W 760 GTCA 820 ATCA I 880	L Q CCTC A S ATCC N P	GGAGG E '77 GCGGG R 83 CAAG7 K	LO GAGGG E (70 CACA) H 1 BO TTGGG L 2	GCTGG(G W ACCTG(N L CGGGC(A G
GTG V CTG L	STTT F ECAG Q	GATCTO D L 730 GACATO T90 GCTCTCO L S 850 GCGGCAO	CTTC F CACA T CGGG	68 CCTGC L 74 AGCCA A 80 GGAGA E 86	O TCGA L D O CCAG T S O CGCT T L O	CAAC N GGAT D	690 CCGT 750 CCAC H 810 GGG 870 GCAG	TGG W CAG	GCTC L GGTG V BAGC S	700 TGGG W 760 GTCA 820 ATCA I 880 ATGG	L Q CCTC A S ATCC N P ACCC N P	GGAGG E 77 GCGGG R 83 CAAG7 K 85	LO GAGGG E 70 CACAI H 130 TTGGG L 100 TTCAI	SCTGGC W ACCTGC N L CGGGCC A G
GTG V CTG L	STTT F ECAG Q	GATCTO D L 730 GACATO T90 GCTCTCO L S 850 GCGGCAO R H	CTTC F CACA T CGGG	68 CCTGC L 74 AGCCA 80 6GAGA E 86 CCCC	TCGAC TCGAG T S CCAG T S CGCT T L CGCT T L	CAAC N GGAT D CAAC	690 CGT R 750 CAC H 810 GGG G 870 GCAG	TGG W CAG	ECTC L EGTG V EAGC ETTC	700 TGGG W 760 GTCA 820 ATCA I 880 ATGG M	L Q CCTC A S ATCC N P ACCC N P	GGAGG E 77 GCGGG R 83 CAAGT K 85 TTTCT	LO GAGGG E (70 CACAL H 1 BO TTGGG L 2 F 1	GCTGG(G W ACCTG(N L CGGGC(A G
GTG V CTG L ATT	STT1 F SCAG Q TGGG	GATCTO D L 730 GACATO 790 GCTCTCO L S 850 GCGGCAO R H 910	CTTC F CACA T GGTG V CGGG	68 CCTGC L 74 AGCCA 80 GGAGA E 86 CCCC P	TCGAC TCGAG CCAG T S CCGCT T L AGAA	CAAC N GGAT D CAAC	690 CGT 750 CCAC H 810 GGG 6 870 GCAG 230	TGG W CAG CCC	ECTC L EGTG V EAGC S ETTC	700 TGGG W 760 GTCA 820 ATCA I 880 ATGG M 940	L Q CCTC A S ATCC N P ACCC N P	GGAGG E 77 GCGGG R 83 CAAGT K 85 TTTCT	LO GAGGG E (70 CACAL H 1 BO TTGGG L 1 OO TTCAL F 1	SCTGG(SW) ACCTG(NL) CGGGC(ACGCC) ACGCC) ACGCC)
GTG V CTG L ATTI	STTT F SCAG Q TGGG G	GATCTO 730 GACATO 790 GCTCTCO L S 850 GCGGCAO R H 910 CCACTTO	CACA T GGTG V CGGG	68 CCTGC L 74 AGCCA A 80 GGAGA E 86 GCCCC P 92 CAGCA	O TCGA L D O CCAG T S O CGCT T L O AGAA Q N O TCCG	CAAC N GGAT D CAAC K	690 CGT 750 CCAC H 810 GGG 6 870 SCAG 230 ACG	TGG W CAG CCC	GCTC L GGTG V BAGC BAGC F	700 TGGG W 760 GTCA 820 ATCA I 880 ATGG M 940 AAAC	L Q CCTC A S ATCC N P ACCC N P TGGC V A AGCG	GGAGG E 77 GCGGG R 83 CAAGT K 85 TTTCT F 95 CAGCG	LO SAGGO E (70 CACA) H 1 BO TTGGO TTGA) F 1 50 CAGA)	ACCCCI
GTG V CTG L ATTI	STTT F SCAG Q TGGG G	GATCTO D L 730 GACATO 790 GCTCTCO L S 850 GCGGCAO R H 910	CACA T GGTG V CGGG	68 CCTGC L 74 AGCCA A 80 GGAGA E 86 GCCCC P 92 CAGCA	O TCGA L D O CCAG T S O CGCT T L O AGAA Q N O TCCG	CAAC N GGAT D CAAC K GTCC	690 CGT 750 CCAC H 810 GGG 670 GCAG 230 ACG	TGG W CAG CCC P	GCTC L GGTG V BAGC BAGC F	700 TGGG W 760 GTCA 820 ATCA I 880 ATGG M 940 AAAC	L Q CCTC A S ATCC N P ACCC N P TGGC V A AGCG	GGAGG E 77 GCGGG R 83 CAAGT K 85 TTTCT F 95 CAGCG	LO SAGGO E (70 CACA) H 1 BO TTGGO TTGA) F 1 50 CAGA)	ACCGCT
GTG V CTG L ATTI	STTT F SCAG Q TGGG G	GATCTO D L 730 GACATO 790 GCTCTCO L S 850 GCGGCAO R H 910 CCACTTO H F	CTTC F CACA T GGTG V CGGG G	68 CTGC L 74 AGCCA A 80 GGAGA E 86 CCCC P 92 CAGCA	O TCGA L D O CCAG T S O CGCT T L O AGAA Q N TCCG I R	CAGO CAAO GGAT CAAO K GTCC S	690 CGT 750 CAC H 810 GGG G 670 GCAG 230 ACG	TGG W CAG CCC P GGG	ECTC L EGTG V BAGC ETTC F BAGC	700 TGGG W 760 GTCA 820 ATCA I 880 ATGG M 940 AAAC K	L Q CCTC A S ATCC N P ACCC N P TGGC V A	GGAGG E 77 GCGGG R 83 CAAGT K 85 TTTCT F 95 CAGCG	LO GAGGG E (70 CACA) H 1 BO TTGGG L 2 F 1 50 CAGA)	GCTGG(GCTGG) ACCTG(A G AGGCC) A G AGGCCI A R
GTG V CTG L ATTI I GAG	STTT F GCAG Q TGGG G GGTC V	GATCTO D L 730 GACATO 790 GCTCTCO L S 850 GCGGCAO R H 910 GCACTTO H F	CTTC F CACA T GGTG V CGGG G	68 CTGC L 74 AGCCA 80 GGAGA E 86 CCCC P 92 CAGCA	O TCGA L D O CCAG T S O CGCT T L O AGAA Q N O TCCG I R	CAGO S CAAO N GGAT D CAAO K GTCC S	690 CGT 750 CAC H 810 GGG G 870 SCAG 230 ACG T	TGG W CAG CCC P	SAGC FAGC SAGC	700 TGGG W 760 GTCA 820 ATCA I 880 ATGG M 940 AAAC K	L Q CCTC A S ATCC N P ACCC N P TGGC V A AGCG Q R	GGAGG E 77 GCGGG R 83 CAAGT K 89 TTTCT F CAGCG	LO GAGGG E (70 CACA) H 1 BO TTGGG L 2 F 1 GO CAGA)	GCTGG(W ACCTG(L CGGGC(A G AGGCCI A A ACCGCT
GTG V CTG L ATT I GAG	STTT F SCAG Q TGGG G G G G G G G	GATCTO D L 730 GACATO 790 GCTCTCO L S 850 GCGGCAO R H 910 GCACTTO H F	EACA T EGGG G ECGG R	68 CTGC L 74 AGCCA A 80 GGAGA E 86 GCCCC P 92 CAGCA	O TCGA L D O CCAG T S O CGCT T L O AGAA Q N O TCCG I R	CAGO CAAO GGAT CAAO K GTCC S CCTG	690 CGT R 750 CAC H 810 GGG G 870 SCAG 730 ACG T 990 SCGG	TGG W CAG CCC P GGG S	SGTG V SAGC STTC F SAGC	700 TGGG W 760 GTCA 820 ATCA I 880 ATGG M 940 AAAC K 1000 AACG	L Q CCTC A S ATCC N P ACCC N P AGCG Q R	GGAGG E 77 GCGGG R 83 CAAGT K 89 TTTCT F 95 CAGCG	LO GAGGO E 70 CACAL H 130 CTGGO CTGGO CTGA CAGAL O LO	ACCGCI
GTG V CTG L ATTI I GAG	STTT F SCAG Q TGGG G G G G G G G G G	GATCTO D L 730 GACATO 790 GCTCTCO L S 850 GCGGCAO R H 910 GCACTTO H F	EACA T EGGG G ECGG R	68 CTGC L 74 AGCCA A 80 GGAGA E 86 CCCC P 92 CAGCA S	O TCGA L D O CCAG T S O CGCT T L O AGAA Q N O TCCG I R	CAACO N CAACO K GTCC S CCTC	690 CGT 750 CCAC H 810 GGG 6 870 SCAG 730 ACG T 990 GCGG	TGG W CAG CCC P GGG ATG	GCCC.	700 TGGG W 760 GTCA 820 ATCA I 880 ATGG M 940 AAAC K 1000 AACG	L Q CCTC A S ATCC N P ACCC V A AGCG Q R TGGC V A	GGAGG E 77 GCGGG R 83 CAAGT K 89 TTTCT F 95 CAGCG	LO GAGGG E (70 CACA) H 1 BO CTGGG L 7 CTCA) F 1 GO CAGA) N 8	CCGCT

3/20

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. Arch	ccc	TGG(30 A	CTC	TCA	GCC	ATG	CAC	GGA	CTC	GTT	TCC	AGA	GGT	AAT	TAT	GAG	CGCC	TAC
. 11	GGC	169		010	1	700	, , , , , , , , , , , , , , , , , , ,		171	0		17	20		1	730		1	740
CX	ccc	YCC.	, O - C A	CCC	AGĈ	CCT	GGG	AGG	AAG	GGG	GCG			GGG	GTG	GGC	ACA'	TTGG	TGT
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<u></u>	270			U. L.											-				
		18	1 በ]	820).				•								

FIG. 2-2

PTQLNAISVLYFDDS
SNVILKKYRNMVVRA

10. The invention of claim 1 or 2 wherein the amino acid sequence of each of said subunit comprises (Seq. ID No. 5):

OP1-16A

- 24 I 70 Y H A P V P P. E N 110 130 R K K C. H. G
- The invention of claim 1 or 2 wherein said protein has an apparent molecular weight of about 30 kD when oxidized, as determined by comparison to molecular weight standards in SDS-polyacrylamide gel electrophoresis.
- 12. The invention of claim 1 or 2 wherein said protein has an apparent molecular weight of about 36 kD when oxidized, as determined by comparison to molecular weight standards in SDS-polyacrylamide gel electrophoresis.

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